REMARKS

This Amendment responds to the Office Action mailed May 4, 2009. With this submission, claims 1-5 and 7-8 are pending; claims 3-5, 7 and 8 are under consideration; and claims 1-2 are withdrawn.

Reconsideration and withdrawal of the rejections made in the above-referenced Office Action are respectfully requested in view of the following remarks.

Telephone Interview

Applicants thank the Examiner for the courtesies extended to the undersigned attorney, Sean Myers-Payne, during a telephone interview on August 3, 2009.

The undersigned attorney proposed during the interview the amendment that is being made herein. The undersigned pointed out that the Examiner had been giving patentable weight to the preamble of the claim, which recites a diagnostic method "for malignant melanoma," and the evidence for this conclusion was the Examiner's rejections including art allegedly showing the relationship between GPC3 and melanoma. The undersigned suggested that the present amendment be made to make clear that the diagnostic method was being performed on a sample from a subject believed to be at risk of malignant melanoma. The undersigned further noted that the amendment would place the claims in better form for appeal by removing any possible uncertainties or ambiguities about what the claim was intended to cover.

The Examiner noted that the proposed amendment would not likely overcome the rejection under 35 U.S.C. § 103. The undersigned stated that Applicants and the Examiner could disagree about whether the claims overall were obvious in view of the art, but submitted that entry of the proposed amendment was still favored because it would place the claims in better form for appeal.

The Examiner appeared favorably inclined to enter the proposed amendment for purposes of putting the claims in better form for appeal.

Information Disclosure Statement

The Office Action states that while the Information Disclosure Statement of January 6, 2009 has been considered, one of the documents, the English language Abstract for EP0561183, has been lined through. The Office has lined through the document allegedly because Applicants did not provide a copy.

In response, Applicants submit that a copy of the initialed and signed Form PTO-1449 was not included with the Office Action. Accordingly, Applicants representative called the Examiner to request that she provide a copy, which was sent by facsimile May 28, 2009 and has been received. Applicants note that a copy of the initialed and signed Form PTO-1449 is present in the Image File Wrapper. Applicants further note that the initialed and signed Form PTO-1449 indicates that the Examiner considered the lined through document, which had, in fact, been provided with the papers submitted January 6, 2009. Applicants thank the Examiner for her helpfulness in clarifying the record.

Examiner's Note

The Office Action states that a revised copy of the Form PTO-892 from the Office Action dated June 17, 2008 has been attached in which the publication date for Reference V has been corrected. In particular, the publication date of the Nakatsura et al. document (Reference V), made of record on the Form PTO-892 mailed May 4, 2009, is incorrect. Applicants submit that the publication date of the Nakatsura et al. document (*Clinical Cancer Research* Vol. 10, pages 6612-6621) is October 1, 2004 – and not October 4, 2004 – as listed on the Form PTO-892. Accordingly, Applicants respectfully request that the Office correct the publication date for the Nakatsura et al. document (Reference V).

Claim Rejections – 35 U.S.C. § 103(a)

The Office Action maintains the rejection of claims 3-5 and 7, and extends the rejection to new claim 8, under 35 U.S.C. § 103(a), as allegedly unpatentable over Katagiri et al. (U.S. Patent Application Publication No. 2003/0165954) in view of Desai et al. (*J. Med. Genet.* **35**:476-481, 1998) as evidenced by Nakatsura et al. (*Clin. Can. Res.* **10**:6612-6621, 2004). In

particular, the Office has repeated the text of the maintained rejection, and indicated that it has not found the previously-filed arguments persuasive. Specifically, the Office Action states that Katagiri et al. teaches detecting the level of expression of one or more drug sensitivity genes such as GPC3 comprising detecting the level of mRNA with a nucleic acid probe or detecting the level of polypeptide with an antibody specific to the polypeptide. The Office Action also states that Katagiri et al. does not disclose that GPC3 expression is associated with skin cancers such as melanoma. For this missing feature, the Office relies upon Desai et al. as evidenced by Nakatsura et al., which allegedly teach that (1) "GCP3 [sic] may be related to a class of skin-related disorders" and (2) GPC3 expression is an inherent characteristic of melanoma.

In response, Applicants respectfully submit that the claimed invention is not unpatentable over Katagiri et al. in view of Desai et al. as evidenced by Nakatsura et al. In particular, Applicants submit that the claimed invention is not unpatentable over the cited documents based at least upon the grounds set forth in Applicants' submission of January 6, 2009.

Initially, with regard to the Nakatsura et al. document, Applicants requested that the Examiner review the verified translation of Japanese foreign priority document JP 2003-368725, filed October 29, 2003 to ascertain its impact on the outstanding rejection. Applicants further submitted that to the extent that the rejection relies on Nakatsura et al., its removal as prior art by submission of the translated priority document rendered moot the entire rejection.

Though not specifically stated, it appears from the content of the Final Office Action, that the Office has determined that Applicants' priority document is sufficient to antedate Nakatsura et al. In this regard, rather than explaining why Applicants' priority document fails to antedate Nakatsura et al., a question which Applicants specifically asked the Office to consider, the Action simply reiterates a point raised in the prior Office Action, i.e., that MPEP 2124 and 2131.01 support the proposition that references relied upon to demonstrate a universally known fact need not be available as prior art. (Final Office Action, page 7, first full paragraph.) Thus, Applicants respectfully submit that Nakatsura et al. is not available as prior art.

Applicants note that the Office Action submits that Nakatsura et al. is not relied upon as prior art, but rather, to "show that missing descriptive matter in the Desai reference is

'necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill in the art.'" (Office Action, page 7, first full paragraph, citations omitted.) However, Applicants respectfully submit that this characterization fails to give Nakatsura et al. the credit it deserves in supporting this rejection. To be quite clear, Nakatsura et al., entitled "Identification of Glypican-3 as a Novel Tumor Marker for Melanoma," and authored by the present inventors (among others), very clearly discloses the discovery that is at the heart of the present invention – that glypican-3, or "GPC3," is a novel tumor marker for melanoma. Applicants respectfully submit that the Office's characterization masks its true role in the rejection as the sole source of motivation and/or expectation of success, two requirements to establish a *prima facie* case of obviousness.

To understand the importance of Nakatsura et al. in the rejection, it is important to recognize what is lacking from Katagiri et al. and Desai et al., and thereby understand what deficiencies Nakatsura et al. satisfies. Katagiri et al. discloses a system and method for screening drugs that are intended to be effective for specific types of patients and cancers. In paragraphs [0213] to [0219], Katagiri et al. describes how an anticancer agent is administered to a cancer-implanted mouse, and determines the expression ratio of genes that relate to the anticancer agent, so that sensitivity to the anticancer agent can be evaluated. As described in paragraph [0082] of Katagiri et al., the tumor marker in Katagiri et al. means "a drug sensitive gene," the expression of which correlates with the sensitivity of tumor to the anti-cancer agent. In other words, the marker of Katagiri et al. is a marker of the sensitivity of the cancer (which was already formed) to the anti-cancer agent.

The cancers recited in the Examples of Katagiri et al. (paragraph [0250]) are glioblastoma, neuroblastoma, small-cell lung carcinoma, choriocarcinoma, breast cancer, pancreatic cancer, stomach cancer, and ovarian cancer. Melanoma is not recited, nor are any experimental results for melanoma presented. Indeed, the Office concedes that Katagiri et al. fails to teach GPC3 expression is associated with skin cancers such as melanoma.

The only mention of GPC3 in Katagiri et al. is as one of 142 genes that is sensitive to adriamycin, an anti-cancer drug.

Simply stated, there is nothing in Katagiri et al. that suggests any correlation between melanoma and GPC3, and there is certainly nothing in Katagiri et al. that suggests a diagnostic method for melanoma using GPC3. On page 6 of the Action, the Office asserts that "Katagiri recognized GPC3 expression correlated with many cancers and the means for diagnosing those cancers using GPC3 as a tumor marker. Katagiri also disclosed kits for detecting cancers comprising an antibody for GPC3 protein and probes for detecting mRNA for GPC3." (First and second sentences under "Response to Arguments.") In response, Applicants respectfully submit that these statements do not find support at all in Katagiri et al., and that if the Office maintains this rejection, Applicants invite the Office to explain how Katagiri et al. stands for those propositions.

Turning to Desai et al., Applicants have previously noted that Desai et al. discloses phenotypic features in juvenile polyposis (JP). Desai et al., like Katagiri et al., is silent with regard to the use of GPC3 expression detection for malignant melanoma. Desai et al. does disclose that one patient with JP was also found to have "many of the features" of Simpson-Golabi-Behmel (SGB) syndrome, a known X-linked condition of variable mental handicap with overgrowth, macrocephaly, hypertelorism, polydactyly, rib abnormalities, and occasionally cleft palate (page 479, 2nd column, first paragraph). Desai et al. further discloses that tests for germline mutations in the GPC3 gene – not detection of GPC3 expression – should allow for the detection of SGB – *not JP or melanoma* – in the cohort studied (page 479, 2nd column, first paragraph).

With respect to Desai et al., the Action states that the "Examiner has identified a reference . . . showing a strong correlation between GPC3 expression and skin-hyper pigmentation disorders which involve hyperproliferation, e.g., a subset of juvenile polyposis patients having the GPC3-associated disorder Simpson-Golabi-Behmel (SGB) syndrome." After noting that Applicants' claims are open to a number of different diagnostic methods, the Action states that "Desai's teaching to identify gene mutations would be overlapping for the method for detecting and measuring GPC3 expression using the unidentified antibody, the unidentified probe or the unidentified primer as instantly claimed." (Paragraph spanning pages 6-7.)

Even taking Desai et al. in a light most favorable to the rejection, Applicants submit that Desai et al. does not teach or suggest the missing features of Katagiri et al. Desai et al. may teach testing for the presence of GPC3 mutations, but it does so with an intention of detecting SGB syndrome – not melanoma. There is simply nothing in Desai et al. that would suggest any relationship between GPC3 and melanoma.

Thus, to summarize, Desai et al. teach testing for the presence of GPC3 mutations to detect SGB syndrome – not melanoma. Katagiri et al. teach that GPC3 is a gene that is sensitive to adriamycin, but make no mention of any correlation of GPC3 expression in melanoma. Thus, the two pieces of prior art relied upon by the Office fail to disclose any relationship between GPC3 and melanoma. There is nothing in either document, or in the two documents combined, that would suggest a diagnostic test for melanoma comprising detecting or measuring GPC3 in a sample from a subject believed to be at risk of malignant melanoma. Still further, there is nothing in Katagiri et al. or in Desai et al. – alone or in combination – that would lead to any modification of either teaching so as to arrive at the present invention.

Applicants also respectfully note that, given that neither Katagiri et al. nor Desai et al. teach any correlation between melanoma and GPC3, there cannot be any possible expectation of success in the present method base on those teachings. That is, a person skilled in the art could not possibly read Katagiri et al. and Desai et al. and conclude that there could be any success whatsoever in a diagnostic test for melanoma comprising detecting or measuring GPC3 in a sample from a subject believed to be at risk of malignant melanoma.

Returning now to Nakatsura et al., one can easily see its importance in the rejection – it is the sole basis for the connection between melanoma and GPC3, and is the sole source of both motivation and expectation of success. However, Applicants respectfully submit that the Office may not rely on non-prior art to establish critical elements of an obviousness rejection, including motivation and expectation of success. As noted above, Nakatsura et al. clearly teaches a correlation between melanoma and GPC3, and thus would be eligible for inclusion in a properly constructed obviousness rejection *if it were prior art*. But, as also noted above, Nakatsura et al. is not prior art and the Office is not entitled to rely on it to establish motivation or expectation of success.

Applicants respectfully submit that Katagiri et al. and Desai et al., in any combination, fail to render obvious the presently claimed invention, and that the Office's reliance on Nakatsura et al. to remedy any deficiency of Katagiri et al. and Desai et al. is improper. Applicants respectfully request withdrawal of the rejections of record.

CONCLUSION

In view of the foregoing, the Examiner is respectfully requested to reconsider and withdraw the rejections of record, and allow all the pending claims.

Applicants also respectfully request that the Office enter the present amendment, as it places the claims in better form for appeal.

No additional fee is believed due at this time. If, however, any additional fee is necessary to ensure consideration of the present amendment, including any fee necessary for an Examiner's amendment, the Patent and Trademark Office is hereby authorized to charge the same to Deposit Account No. 19-0089.

Should there be any questions, the Examiner is invited to contact the undersigned at the below listed telephone number.

Respectfully Submitted,
Yasuharu Nishimura et al.

Bruce H. Bernstein
Reg. No. 29027 42,920

August 4, 2009
GREENBLUM & BERNSTEIN, P.L.C.
1950 Roland Clarke Place
Reston, VA 20191
(703) 716-1191